II. CLAIM OBJECTIONS ARE OVERCOME BY CLAIM AMENDMENTS

Claims 4, 5, 13, 14, 18, 19 and 27 - 37 were objected to under 37 C.F.R. §1.75(c) as being in improper form because a multiple dependent claim cannot depend from any other multiple dependent claim and because a multiple dependent claim should refer in the alternative only to other multiple dependent claims. For that reason, the aforementioned claims were not further treated on the merits. Office Action, page 4.

Applicants amended claims objected to in accordance with the Examiner 's helpful suggestion. Applicants respectfully request consideration of these claims on the merits.

Applicants also amended claims 1 and 15 to incorporate claims 2, 3, 16, 17, respectively, into claims 1 and 15. New claims 38-40 are directed to additional details of the invention.

III. ORIGINAL CLAIMS 1-3 AND 15-17 SATISFIED THE REQUIREMENTS OF §112. AMENDED CLAIMS CONTINUE TO SATISFY THAT REQUIREMENT.

Claims 1-3 and 15-17 were rejected under 35 U.S.C. § 112, first paragraph ("§112, first paragraph") because, allegedly, they contained subject matter that was not described in the specification sufficiently to enable a person skilled in the art to which it pertains, or with which it is most nearly connected, to make an/or use the invention.

In support of the enablement rejection, it was stated that the claims were directed to a method for determining risk of an individual developing primary or metastatic cancer, including a method for assessing a patient's risk for developing metastatic cancer that may develop secondarily or independently of a primary cancer. It was stated that the claims include a method for diagnosing any type of primary or metastatic cancer in an individual and the determination of a single parameter corresponding to the concentration of TIMP-1 in a sample of a bodily fluid. Office Action, pages 4-5. Examples provided in the specification were discussed and the Examiner pointed out that some of them do not support the full scope of the claimed invention. For instance, according to the Examiner , Example 7 indicates that the concentration of free TIMP-1

lacks diagnostic value and thus cannot be used to determine the likelihood of cancer in an individual. Office Action, page 6. It was also stated that Example 10 indicates that Applicants' method cannot be used to determine the likelihood of a primary, non-malignant breast cancer in an individual. *Ibid.* It was concluded that the specification's teachings cannot be extrapolated to the full scope of enablement of the claims and therefore a skilled person could not practice the invention with a reasonable expectation of success without performing extensive and undue experimentation. Office Action pages 6-7.

A number of publications were also cited for the proposition that many tumor-associated markers, particularly when used alone and under certain conditions, are diagnostically unreliable. According to the text in the Office Action, TIMP-1 is one of such markers. Office Action, pages 8-13. Based on a summary of such publications, it was asserted that TIMP-1 alone, free TIMP-1 or samples of TIMP-1 acquired in some reagents but not in others (all covered by Applicants' claims) are not likely to be reliable predictors of the likelihood of development, recurrence or metastasis of any cancer.

Applicants respectfully traverse this rejection. Applicants respectfully submit that claims 1-3 and 15-17, as filed, were enabled by the specification. Nonetheless, in the interest of advancing and expediting prosecution of the application, Applicants amended these claims. The amended claims continue to be enabled by Applicants' disclosure.

At the outset, Applicants respectfully point out that the Examiner 's following statements at page 7 of the Office Action are misplaced: "...it is noted the claims are drawn to a method for determining whether an individual or a patient has cancer or will have cancer. However it is also noted that the specification does not exemplify the claimed method." and "...there is no factual evidence of record that indicates that the concentration of TIMP-1 in a bodily fluid of an individual or patient correlates with the incidence of cancer in said individual or patient." *Ibid.*

Applicants submit that there is no legal precedent that requires them to submit experimental data to verify that their invention is operable in order to satisfy the enablement requirement. It is well settled that the enablement requirement may be

satisfied in any manner that would teach those of ordinary skill in the art how to make and use the invention without undue experimentation. Experimental work, while helpful in this regard, is not a prerequisite in meeting the enablement requirement.

Nonetheless, Applicants have shown in the specification that their invention can be used to determine the likelihood that an individual or a patient has or will have primary colorectal cancer or metastatic breast cancer. Persons of ordinary skill and the art familiar with Applicants' specification and particular examples, would readily understand how to use Applicants' claimed method to determine the likelihood that a patient may develop primary colorectal cancer or metastatic breast cancer.

One of the basis for the assertion in the Office Action of an insufficient guidance to enable a person skilled in the art to practice the invention with a reasonable expectation of success is that the threshold value of the concentration of TIMP-1 that can be used to discriminate the patient who has primary or metastatic cancer from a disease-free individual is not disclosed. Office Action, page 7. This appears to be a requirement that Applicants must disclose in their specification a precise value for TIMP-1 concentration which would be used for any patient, and any cancer (covered by claims) as a bright line test to determine, always with a 100% certainty, that an individual has or is likely to have cancer. However, the claimed invention is not directed to such a single, precise value of TIMP-1 concentration. A relevant threshold value of total TIMP-1 concentration (or discriminating value as defined in the claims) can be selected from ROC (Receiver Operating Characteristics) curves which are disclosed in the application. These curves give the correlation between sensitivity and specificity and the sensitivity/specificity for any selected total TIMP-1 threshold value can be derived from the curves. A threshold value resulting in a high sensitivity results in a lower specificity and vice versa. For example, if one wishes to detect all colorectal cancers with a high degree of certainty, then the specificity will be lower and some false positives are likely to be included. If one wishes to be relatively certain that only malignant colorectal cancers will be detected, then a number of non-malignant colorectal cancers are likely not to be identified.

Each individual diagnostic department thus can determine which level of sensitivity/specificity is desirable and how much loss in specificity is tolerable. The chosen threshold level could be dependent on other diagnostic parameters used in combination with the Applicants' claimed method by the individual diagnostic department, e.g. the use of coloscopy.

The statement on page 7 of the Office Action that the specification indicates "that this range of values [the threshold value] will vary experimentally", apparently results from a misunderstanding of the paragraph in the specification (page 5, lines 5 and 8-10) because this possibility of variation in the values is discussed exactly in the context of the discussion of a choice of a threshold value (or discriminating value). The variation is not caused by variation in the methods used to determine the TIMP-1 level due to the included internal standard which excludes inter-assay variations. Furthermore, inter-patient variations in TIMP-1 levels have been included in the calculation of the ROC curves.

A noteworthy fact in this respect is that a consensus threshold value for the highly acknowledged PSA (Prostate Specific Antigen) does not exist in the art even though this marker is widely used.

In support of the lack of enablement rejection, it was also stated that the specification only teaches measuring TIMP-1 in plasma, and then only of "plasma samples acquired in EDTA". Office Action, page 10. Applicants respectfully point out that Example 1 shows a correlation between plasma samples acquired both in EDTA and citrate. Also, see e.g. Figure 5b which additionally gives a correlation coefficient between EDTA and citrate samples of 0.93.

Numerous arguments (many relying on published literature) were presented in the Office Action to support an assertion of the lack of usefulness of TIMP-1 as a diagnostic marker. Applicants respectfully submit that this apparent state of the art (prior to Applicants' invention) supports the novelty, non-obviousness and enablement of their invention. This is underscored by a statement on page 12 of the Office Action: "... but it is doubtful that one [skilled in the art] would conclude that measuring the level

of TIMP-1 alone would be as effective". If this reflects the accepted consensus of state of the art in this technology by the scientific community, the invention and experimental results Applicants disclosed in the application are truly novel, unobvious and enabled to a person skilled in the art.

The fact that other authors of scientific papers speculate that a single diagnostic marker will never suffice in giving a significant diagnostic response is contradicted by the Applicants' invention described in the specification, wherein Applicants disclose a highly diagnostic value of a single diagnostic marker, TIMP-1, which certainly can stand alone but of course could be combined with other markers (as also disclosed in the application). Another example of a known and widely used single diagnostic marker is the measurement of total PSA in the diagnosis of prostate cancer.

Reliance in the Office Action on literature references, such as Michael et al., which teaches that TIMP-1 is largely absent from small-cell lung cancers and Arnold et al. which teaches that "the vast majority of some types of tumors whether metastatic or not are entirely devoid of TIMP-1" (Office Action, pages 9 and 10) underscores the uniqueness of the Applicants' claimed method and its specificity for colorectal cancer and metastatic breast cancer. When a sample shows a required level of TIMP-1 (given from the ROC curve), the Applicants' claimed method is likely to indicate that this TIMP-1 level is not caused by other "non-specific" tumors.

Tockman et al. was cited for its alleged teaching of the "considerations necessary in bringing a cancer biomarker...to successful clinical application". Office Action, page 11. One of the considerations is to "confirm marker predictive value in prospective population trials" *Ibid.* The discussion of this reference is concluded by stating:

> Clearly, prior to the successful application of newly described markers, validation against acknowledged disease end-points must occur and the markers' predictive value must be confirmed in prospective population trials (page 2716, column 2).

Office Action, page 12.

If this is the standard applied to Applicants' specification to determine the presence (or absence) of enabling disclosure in the specification (which appears to be the case), it squarely contradicts the standard established by numerous Federal Circuit (and other court) decisions for determining if a specification meets the enablement requirement of the statute. Courts have consistently held that the enablement requirement is satisfied if the scope of claims in question is enabled so that a person of ordinary skill in the art would be able to make the invention without undue experimentation. The question of undue experimentation is a matter of degree. If some experimentation is necessary, it does not preclude enablement, so long as such experimentation is not unduly extensive, *PPG Industries, Inc. v. Guardian Industries Corp.*, 37 U.S.P.Q.2d 1618, 1623 (Fed. Cir. 1996). In the *PPG Industries* case, the court also held that

> "[W]here the specification provides 'guidance in selecting the operating parameters that would yield the claimed result, it is fair to conclude that the experimentation required to make a particular embodiment is not 'undue.'"

PPG Industries, Id. at 1624.

Similarly, in another case (*John Hopkins University v. Cellpro, Inc.*, 47 U.S.P.Q.2d 1705 (Fed. Cir. 1998)), the Federal Circuit found enablement in a patent specification disclosing only one method of producing one antibody for a claim directed to a broader genus of antibodies. The court made that finding based, *inter alia*, on a declaration submitted by an opposing party's (a defendant in a patent infringement litigation) expert that the disclosure in the specification of the patent was sufficient for him to make antibodies other than that disclosed in the specification. The expert stated in the declaration that he had to use some experimentation to obtain that result. The court concluded that such routine experimentation does not constitute undue experimentation. *John Hopkins, id* at 1718-19.

Similarly, in this application, Applicants have provided numerous examples of determining a parameter representing the total concentration of TIMP-1 in bodily fluid

samples in connection with gastrointestinal and metastatic breast cancers and the use of that parameter as an indicator of the likelihood of an individual having a gastrointestinal or metastatic breast cancer. Applicants have satisfied the enablement requirement.

If the standard based on Tockman et al. were used, it would substantially correspond to a standard necessary for an FDA approval, which of course is not necessary to meet the standard of Section 112, first paragraph. Indeed, if it was necessary, very few, if any, patent applications or patents for a diagnostic marker or methods, could satisfy such an FDA standard. Patents issued for PSA support Applicants' position that the enablement requirement is not governed by FDA rules.

It was also stated in the Office Action that "one skilled in the art would not accept the assertion that the invention can be used to diagnose any type of cancer, including colorectal and breast cancer". Office Action, page 13. Applicants wish to advise that scientific community has expressed significant interest in their invention, which rebuts the aforementioned statement. The statement that "one skilled in the art would not accept the assertion that the invention can be used to assess an individual's risk for developing cancer because the role of TIMP-1 over-expression in pathogenesis and the etiology of cancer is still not complete" (*Ibid.*) is misplaced. The exact role of TIMP-1 is irrelevant when using it as a diagnostic marker. The role of TIMP-1 is only relevant when trying to understand the pathogenesis and/or etiology of cancer, e.g. in the search for cancer treatment. Applicants' claimed invention is not directed to those aspects of cancer research.

Finally, the Examiner cited a part of an Abstract of a scientific paper by one of the inventors: "Additional studies are needed to validate the clinical usefulness of plasma TIMP-1 measurements". Office Action, page 13. Even if this statement is a very common statement in the language of scientific papers, it was taken out of context, insofar as it is related to prognosis and has nothing to do with diagnosis. In fact, the full Abstract supports Applicants' assertion that their specification is enabling. In the

sentence preceding that cited in the Office Action, the authors stated "...plasma TIMP-1 levels were found to predict prognosis of colorectal cancer patients."

IV. ORIGINAL CLAIMS 1-3 AND 15-17 WERE DEFINITE UNDER §112, SECOND PARAGRAPH. AMENDED CLAIMS CONTINUE TO BE DEFINITE.

Claims 1-3 and 15-17 were rejected as vague and indefinite, and therefore failing to satisfy the definiteness standard of 35 U.S.C. §112, second paragraph ("Section 112, second paragraph") allegedly because of the presence of several different phrases. Such phrases included "a method for determining whether an individual is likely to have cancer" (in claims 1-3) or "a method for determining whether a patient who has been treated for primary cancer is likely to have metastatic cancer" (claims 15-17). It was explained that these phrases render claims vague and indefinite because it cannot be determined whether they are directed to a method for determining the probability that an individual or patient will develop primary or secondary metastatic cancer or to a method for determining if an individual or patient already has such primary or secondary metastatic cancer.

With respect claim 15, it was also asserted that it is unclear whether it requires the patient to have been treated successfully or unsuccessfully for primary cancer and, therefore, it is unclear whether the claim requires the patient to be likely to have metastatic cancer that developed secondarily to the primary cancer or independently. It was concluded that for the above reasons, persons ordinarily skilled in the art would not be reasonably apprised of the metes and bounds of the invention. Office Action, page 14.

Applicants respectfully traverse this rejection. It is well established that claims are definite if, read in the light of the specification, they "...reasonably apprise those skilled in the art both of the utilization and scope of the invention, and if the language is as precise as the subject matter permits." *Andrew Corp. v. Gabriel Electronics, Inc.,* 6 U.S.P.Q.2d 2010 (Fed. Cir. 1988). (Quoting *Shatterproof Glass Corp. v. Libbey-Owens Co.* 225 U.S.P.Q. 634 (Fed. Cir.), *cert. dismissed* 474 U.S. 976 (1985)). The claim terms at issue in the *Andrew* decision were "approach each other", "close to",

"substantially equal" and "closely approximate". The Federal Circuit held that claims containing such terms were definite. The Federal Circuit also pointed out that in several previous decisions, it held the following claim terms definite "close proximity" (*Rosemount, Inc. v. Beckman Instruments, Inc.*, 221 U.S.P.Q. 1 (Fed. Cir. 1984)) and "substantially equal" (*Seattle Box Co. v. Industrial Crating & Packing*, 221 U.S.P.Q. 568 (Fed. Cir. 1984)). In the latter case, the court elaborated that "substantially equal" is a term of degree and its acceptability depends on whether or not "one of ordinary skill in the art would understand what is claimed...in light of the specification", even if experimentation may be needed.

Similarly, in Applicants' claims, the criticized phrases, when read in light of the specification, readily apprise those skilled in the art of the metes and bounds of Applicants' claimed invention. The specification teaches those of ordinary skill in the art that the discriminating value recited in the claims has been determined by measuring a parameter (representing the total concentration of TIMP-1 in a body fluid sample) in both healthy control population and a population with known cancer. This determines the discriminating value which identifies the cancer population with either a predetermined specificity or a predetermined sensitivity, page 4, lines 21-25. The examples and detailed description of the invention provide additional detailed explanation of Applicants' claimed method. Thus, the method provides an indication of the likelihood that the patient has gastrointestinal cancer (claims 1-3) or metastatic breast cancer (claims 15-17). That indication can be ascertained either with a high degree of specificity or a high degree of sensitivity, depending on the discriminating value selected. As discussed above, the discriminating value can be selected by persons of ordinary skill in the art from the ROC curves, the method for preparation of which is also disclosed in the specification.

Claims 1-3 and 15-17 were also rejected as indefinite due to the presence of the term "first" parameter. The amended claims do not contain that term, thereby rendering this ground of rejection moot.

Another reason for rejecting the claims as indefinite was the presence of the term "high likelihood", allegedly by a relative term which renders claims indefinite. It was asserted that the specification does not provide a standard for ascertaining the requisite degree, which makes it impossible to determine how likely it is that an individual or a patient will have primary or metastatic cancer at the present time or in the future if the parameter is at or beyond a discriminating value. Office Action, pages 14-15. A related reason for rejecting claims as indefinite was predicated on the presence of the terms "predetermined specificity or a predetermined sensitivity" in claims 3 and 17. Office Action, page 16. As discussed above, the Applicants' method as disclosed in the specification, enables a person using that method and performing the diagnosis to exercise his or her professional judgment in selecting the degree of specificity/sensitivity desirable and the threshold level of TIMP-1, determined from the ROC curve. The specificity/sensitivity value is determined in the exercise of such judgment and cannot be given a fixed number because it may (and in fact, it is likely to) vary depending on the overall scope of the diagnostic procedure. Just as "closely approximate", and "substantially equal" were found definite in *Andrew Corp, supra*, and the term "close proximity" was found definite in a court decision discussed in *Andrew Corp*, so are Applicants' terms "high likelihood" and "predetermined specificity" or "predetermined specificity or sensitivity" definite when viewed in light of the specification.

Claims 1-3 and 15-17 were also rejected due to the presence of the term "a discriminating value", because it was allegedly unclear what value of a first parameter is discriminating. Office Action, page 15. Applicants' amendments of claims 1 and 15 render this rejection moot.

The claims were also rejected as indefinite because, allegedly, it was unclear whether they require the total concentration or merely a part of the total concentration of TIMP-1 in the sample to be determined. Office Action, page 15. Applicants respectfully submit that their original claims were definite. Amended claims continue to be definite.

The claims were also rejected as indefinite due to the recitation in claims 1 and 15 of "in body fluid samples". It was alleged that this phrase renders the claims vague

and indefinite because it is unclear whether they require the "...the body fluid samples to be acquired from sampling the body fluids of the individual or the patient of line 1 in the claims or from sampling the body fluids of a different individual or patient or population of individuals or patients". Office Action, page 15. Applicants submit that in original claims 1 and 15 it was clear that only one individual was referred to and body fluid samples were obtained only from that individual. Nonetheless, in the interest of expediting prosecution, Applicants amended claims which continue to be definite.

Another reason for rejecting the claims was the alleged lack of a positive correlation step clearly relating the method steps in the body of the claim to the preamble thereof. Office Action, pages 15-16. Applicants also respectfully traverse this rejection. Nonetheless, in the interest of expediting prosecution, they have adapted the Examiner's kind suggestion and amended claims 1 and 15 to recite such a correlation.

Claims 3 and 17 were additionally rejected due to the recitation of "said at least one first parameter". Office Action, page 16. Applicants maintain that the original claims were definite. The amended claims continue to be definite.

Claims 3 and 17 were also rejected as vague and indefinite due to the presence of the term "thereby determining the discriminating value" in lines 3 and 4. It was observed that it was not clear whether the "discriminating value" of line 4 was the same as the discriminating value in line 1. Applicants continue to maintain that the original claims were definite. Nonetheless, the claims amended herein to advance prosecution continue to be definite.

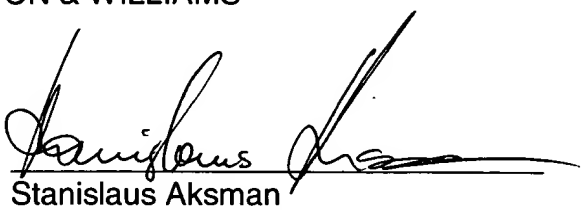
V. CONCLUSION

For all of the reasons discussed above, Applicants respectfully submit that all claims are now in condition for allowance, an indication of which is solicited. In the event that any outstanding issues remain in the application, Applicants would appreciate

the courtesy of a telephone call to their undersigned representative to resolve such issues in an expeditious manner and place the application in condition for allowance.

Respectfully submitted,

HUNTON & WILLIAMS

By: 
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APPENDIX A

I. On page 27, lines 1 - 3, please delete the paragraph and replace it with following replacement paragraph:

The median TIMP-1 level in plasma from healthy donors was 88.6 µg/L with a range of 51.0-156.2 µg/L. There was a highly significant statistical difference in the total plasma TIMP-1 values between the colorectal cancer patients and the healthy blood donors.

II. On page 37, lines 1-4, please delete the paragraph:

[ABSTRACT

The present invention describes a method for determining whether an individual is suffering from cancer by determining a parameter representing the TIMP-1 concentration in body fluid samples from the individual.]

III. On new page 47, please add the following paragraph:

ABSTRACT

The present invention describes a method for determining whether an individual is suffering from cancer by determining a parameter representing the TIMP-1 concentration in body fluid samples from the individual.

APPENDIX B

1. (Once Amended) A method for determining whether an individual is likely to have gastrointestinal cancer, the method comprising determining a [first] parameter representing the total concentration of TIMP-1 in body fluid [samples] sample of said individual, other than blood serum, and indicating the individual as having a high likelihood of having gastrointestinal cancer if the parameter is at or beyond a discriminating value and indicating the individual as unlikely of having gastrointestinal cancer if the parameter is not at or beyond the discriminating value[.], whereby the likelihood that said individual is likely to have gastrointestinal cancer is determined, the discriminating value being a value which has been determined by measuring said parameter in both a healthy control population and a population with known gastrointestinal cancer, thereby determining [the] said discriminating value which identifies the gastrointestinal cancer population with a predetermined specificity and/or a predetermined sensitivity.

[2. A method according to claim 1, wherein the first parameter is the total concentration of TIMP 1.]

[3. A method according to claim 1 or 2, wherein the discriminating value is a value which has been determined by measuring said at least one first parameter in both a healthy control population and a population with known cancer, thereby determining the discriminating value which identifies the cancer population with a predetermined specificity or a predetermined sensitivity.]

4. (Once Amended) A method according to [any of the preceding claims] claim 1, wherein the [at least one first] parameter determined is the value obtained by combining the concentration of total TIMP-1 with the concentration of free TIMP-1.

13. (Once Amended) A method according to [any of the preceding] claims 1, 4 or 5 wherein the individual is a member of an unselected population.

14. (Once Amended) A method according to [any of the preceding] claims 1, 4 or 5 wherein the individual is a member of a population already identified as having an increased risk of developing cancer.

15. (Once Amended) A method for determining whether a patient who has been treated for primary breast cancer is likely to have metastatic breast cancer, comprising determining a [first] parameter representing the total concentration of TIMP-1 in a body fluid [samples] sample of said individual, other than blood serum, and indicating the individual as having a high likelihood of having metastatic breast cancer if the parameter is at or beyond a discriminating value and indicating the individual as unlikely of having metastatic breast cancer if the parameter is not at or beyond the discriminating value[.], whereby the likelihood that said individual is likely to have metastatic breast cancer is determined, the discriminating value being a value which has been determined by measuring said parameter in both a healthy control population and a population with known metastatic breast cancer, thereby determining said discriminating value which identifies the metastatic breast cancer population with a predetermined specificity and/or a predetermined sensitivity.

[16. A method according to claim 15, wherein the first parameter is the total concentration of TIMP-1.]

[17. A method according to claim 15 or 16, wherein the discriminating value is a value which has been determined by measuring said at least one first parameter in both a healthy control population and a population with known metastatic cancer, thereby determining the discriminating value which identifies the metastatic cancer population with a predetermined specificity or a predetermined sensitivity.]

18. (Once Amended) A method according to [any of claims] claim 15 [-17], wherein the [at least one first] parameter determined is the value obtained by combining the concentration of total TIMP-1 with the concentration of free TIMP-1.

27. (Once Amended) A method according to [any of claims] claim 15 [-26], wherein the determination is performed at several time points at intervals as part of a monitoring of a cancer patient after the treatment for primary cancer.

28. (Once Amended) A method according to [any of claims] claim 1 [-14], used for detecting early stage cancer.

30. (Once Amended) A method according to [any of the preceding] claims 1 or 15, wherein the body fluid is selected from the group consisting of blood ([serum and] plasma), faeces, urine and cerebrospinal fluid.

34. (Once Amended) A method according to [any of the preceding] claims 1 or 15, wherein the total concentration determination of TIMP-1 [determination] is performed by means of an immuno assay or an activity assay.

[37. A method according to any of the preceding claims, wherein the cancer type is selected from the group consisting of colon cancer, rectal cancer and metastatic breast cancer, lung cancer, prostate cancer, ovarian cancer, cervical cancer, liver cancer and gastric cancer.]